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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/588,314	06/06/00	HOOKER B	059440/0128

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RICHARD C PEET
FOLEY & LARDNER
WASHINGTON HARBOUR
3000 K STREET NW SUITE 500
WASHINGTON DC 20007-5109

EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/588,314	Applicant(s) HOOKER ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for a typographical error in step (b) where the first parenthesis is missing from "b)".

Claims 1 and 6 are indefinite for the language "an encoding sequence" in step (a) since it is unclear what the metes and bounds of the "encoding sequence" are. It follows from the preamble and step (e) that it must encode human coagulation factor VIII, but as broadly written would encompass any DNA sequence which would encode other proteins than human coagulation factor VIII. Thus it is unclear how "an encoding sequence" having a sequence to any DNA other than a human coagulation factor VIII could allow purification of a human coagulation factor VIII as stated in step (e). Although claim 23, step (a) specifies "a coagulation factor VIII encoding sequence" it does not specify human, and it is likewise unclear how any coagulation factor VIII

encoding sequence from any species could encode a human coagulation factor VIII as claimed in step (g).

Claim 1 lacks antecedent basis for the language "the plurality of transgenic plant cells" in step (e).

Claim 6 is unclear for the language "genetic material encoding the production of the human coagulation factor VIII" in step (b) since genetic material literally encodes proteins, not "the production of ...".

Claim 7 is indefinite for "genomic DNA" as a limitation since it is unclear how you would transform and express an entire genome in a transgenic plant. Further, claim 7 is indefinite for the language "combinations thereof" since it is unclear how to form a combination of cDNA and genomic DNA, ie. what the metes and bounds of the structures of such compositions would comprise.

Claim 8 lacks antecedent basis for the language "in the whole plant."

Claim 11 is indefinite for the language "substantially that of human coagulation factor VIII" since the metes and bounds of the sequence structure of any sequence which is "substantially" the same as human coagulation factor VIII are unclear. Furthermore, the claim is indefinite since such language fails to further limit the scope of the claim since it is unclear whether "substantially" includes other species than human.

Claim 13 lacks antecedent basis for "the B-domain."

Claim 15 is indefinite since it is unclear how a human/porcine factor VIII would still be considered a "human" protein, thus properly depending on claim 6 which specifies human factor VIII.

Claims 16 and 17 are indefinite since it is unclear whether the claimed heavy and light chain proteins are still human, as in claim 6.

Claim 19 lacks antecedent basis for "said transcription promoter" in both lines 2 and 3.

Claim 20 is indefinite for the language "additional regulatory element encoding a signal peptide" since parent claim 18 claims a signal peptide and it is unclear what the metes and bounds of the structure of the composition in claim 20 would be if comprising yet a second, "additional", signal peptide. Claim 20 further lacks antecedent basis for "the transcription promoter and the upstream 5' end of the encoding sequence."

Claim 23, step (d), lacks antecedent basis for "the transgenic plant."

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of expression of a known human or porcine/human chimera coagulation factor VIII in tobacco plants, does not reasonably provide enablement for methods of

expression of any encoding sequence having any modification from any vector in any plant as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-23 are drawn to methods of using a genus of encoding sequences, plant expression vectors and transgenic plants for production of any human coagulation factor VIII, including full length, B-domain deletions, VIIIa, porcine/human recombinants, heavy chain and light chain, including any 'modification' of the encoding sequence. The claims are thus drawn to a breadth of nucleic acid sequences, vector and host cells/plants for expression of any human coagulation factor VIII-type protein or modifications thereof.

The specification as filed discloses use of the ATCC plasmid 39812 encoding the full-length polypeptide of factor VIII from human fetal liver (heavy chain, B-domain and light chain), subcloning into a vector for expression from the promoter CaMV 35S in tobacco plants.

The claims read on a broad scope of methods for expressing any encoding sequence, having any modification for expression in any plant species for extracting a quantity of human coagulation factor VIII. The claims read on any modification of the encoded sequences for recombinant expression in plants, and different modifications were known in the art for expression in different parts of the plant, for instance.

There is unpredictability in the art for expressing genes in different species of organisms, in the instant case, different plant species since recombinant plants operate under different

physiological conditions and the structure of the vector (ie. the strength of the promoter for instance and size of the vector), the location of the vector in the plant, and the composition of the expressed product are all factors which determine the function of a composition *in vivo*. The factors considered unpredictable are (1) the scope of sequences claimed (any sequence), (2) the scope of modifications of said sequences, and (3) use of any plant species for the recombinant expression. Note Cramer et al. (also cited below in the 35 U.S.C. 102 rejection) who teach that "Tobacco is the easiest plant to genetically engineer, is an excellent biomass producer, and is highly reproductive, facilitating rapid scale-up." These factors are all considerations that are not equivalent in other plant species, and thus would not make it predictable to express any protein equivalently in any plant species. Furthermore, absent specific sequence structure (that taught in the specification or the art) for expression of the claimed coagulation factor VIII proteins, one skilled in the art would necessarily practice "trial and error" experimentation to identify, isolate or otherwise make sequences which when encoded would produce the claimed proteins. Note Brenner, Smith et al., Skolnick et al., Bork, Ngo et al., and Wells who teach the unpredictability in the art for anticipation of protein structure/function from any potential identified nucleic acid sequence. In the instant case, the claims read broadly on any sequence which would express human coagulation factor VIII, but neither the specification nor the art teach how one skilled in the art would be able to make or use this scope of sequences for the functions claimed.

Furthermore, claim 7 claims expressing genomic DNA. It is unclear how one skilled in the art would be able to express genomic mammalian genes in plants since it is unclear how they

would be transformed into the plant and further modified in the plant to produce a protein as claimed.

In view of the unpredictability in the art for the breadth of the instant claims, and the lack of guidance in the art for making the claimed scope of sequences for the functions claimed, one skilled in the art would necessarily practice undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cramer et al in view of Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al.

See above for the brief description of the claims. In the above 35 U.S.C. 112, first paragraph, scope of enablement, rejection, it was argued that the claims are only enabled for the scope of expression of known human coagulation factor VIII sequences in Tobacco plants.

Cramer et al. are relied upon to teach bioproduction of human enzymes in transgenic tobacco plants. Specifically, they teach the preference of tobacco plants for transgenic production of human proteins because they are the easiest of the plants to use recombinantly (see page 63, lines 17-bottom of page). Although they teach by way of example human protein C (hPC) expression, they teach the motivation for expression of any potential human therapeutic proteins since "for natural protein products, human tissues (or fluids) are in limited supply, and their use as a source of human protein is further constrained by the potential for contamination by infections agents" (page 62, first paragraph).

Hoeben et al. (IDS Reference A6), Healey et al., Lollar et al., Stein et al. and Lubin et al. are all relied upon to teach human and/or human/porcine chimeras of coagulation factor VIII. Hoeben et al. is further relied upon to teach motivation for recombinant expression of human coagulation factor VIII for use in the treatment of hemophilia.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to recombinantly express human coagulation factor VIII in transgenic Tobacco plants since it was known in the art to recombinantly express human coagulation factor

VIII (see Hoeben et al.) and the use of Tobacco plants was known in the art for expression of human proteins (as taught by Cramer et al.) for therapeutic purposes.

One of ordinary skill in the art would have been motivated to recombinantly express human coagulation factor VIII as taught by Hoeben et al. and would have been motivated to recombinantly express such a therapeutic protein in Tobacco plants as taught by Cramer et al.

One of ordinary skill in the art would have had an expectation of success to recombinantly express human coagulation factor VIII in Tobacco plants since Cramer et al. taught the positive benefits of recombinant expression of human proteins in Tobacco plants and the sequence of human coagulation factor VIII was well known in the art for expression of different forms (as taught by Hoeben et al., Healey et al., Lollar et al., Stein et al. and Lubin et al.) useful for therapeutic purposes in the treatment of hemophilia.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER

M. M. Schmidt
September 30, 2001